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Study Demonstrates Improved Health, Survival In Aged Overweight Male Mice on Resveratrol

Overweight aged male mice whose high calorie (fat) diet was supplemented by resveratrol, a natural compound found in common foods like grapes, wines and nuts, had better health and survival than aged overweight mice who did not receive it, according to a study published online in the Nov. 1 issue of *Nature*. The study was conducted and supported in part by the National Institute on Aging (NIA) of the National Institutes of Health (NIH).

The findings are the first to demonstrate that resveratrol, an activator of a family of enzymes called sirtuins, could affect the health and survival of mammals. The findings build upon previous research on resveratrol, a small molecule produced by certain plants in response to stress. Studies over the last few years have found that resveratrol can extend lifespan in yeast, worms, flies and fish.

The study was a collaborative effort between the laboratories of Rafael de Cabo, Ph.D., at the NIA, David A. Sinclair, Ph.D., at Harvard Medical School and an international group of researchers. "There is currently intense interest in identifying interventions that can be applied to improve health and survival, especially as our society ages. Today's basic science findings are a notable step in this effort," notes Richard J. Hodes, M.D., director of the NIA. "At the same time, it should be cautioned that this is a study of male mice, and we still have much to learn about resveratrol's safety and effectiveness in humans."

The report describes the result of studies of year-old (middle-aged) mice placed on three different diets for six months: a standard mouse diet, a high calorie (fat) diet and a high calorie (fat) diet supplemented with resveratrol. After six months, the scientists observed a clear trend toward increased survival and insulin sensitivity (important for the body's efficient processing of glucose into energy) in the high calorie diet supplemented with resveratrol relative to that seen on the high fat diet without resveratrol supplementation. In the study, resveratrol shifted the physiology of middle-aged mice on a high calorie diet towards that of mice on a standard diet

and increased their survival.

The scientists reported that:

- At 60 weeks of age, the survival curves of the high calorie and the high calorie/resveratrol groups began to diverge, when the resveratrol group began to show a 3-4 month advantage in survival. As the mice aged, the trend continued.
- At 114 weeks, when the mice reached old age, more than half of the high calorie mice died compared to less than a third of the high calorie mice receiving resveratrol. The overweight resveratrol-treated aged mice were healthier than the overweight mice that were not given resveratrol on a number of measures. For example, the untreated high calorie mice had increased plasma levels of insulin, glucose and insulin-like growth factor (IGF) 1 — markers that in humans predict the onset of diabetes — when compared with their overweight counterparts who did receive resveratrol.
- Some of the health-related findings were most evident in the liver of the high calorie mice. At 18 months of age (six months into the study), the livers of the high calorie, untreated mice were twice the size and weight of those of the high calorie/resveratrol animals, whose livers were comparable to the mice on standard diets. The livers of the high calorie, resveratrol-treated mice were more normal on a cellular level as well. They had considerably more mitochondria (cell structures that metabolize glucose and other sugars) than those of the untreated high calorie group and resembled the levels of mice on the standard diet.
- Gene expression analysis in livers of these aged and overweight mice indicated that resveratrol modified some of the known metabolic pathways that are also affected by caloric restriction. Pathways are a series of chemical reactions that take place in living tissue
- A test of motor function determined the effect of resveratrol on physical performance with age. Tests on a rotating device to measure balance and motor coordination showed that the resveratrol-fed overweight mice maintained their performance on one laboratory measure of motor skills.

“After six months, resveratrol essentially prevented most of the negative effects of the high calorie diet,” de Cabo concludes. “There is a lot of work ahead that will help us better understand resveratrol’s roles and the best applications for it.”

De Cabo and Sinclair did not observe toxic effects of resveratrol on the mice at the doses studied. However, de Cabo emphasized, the safety and effectiveness of the substance for humans to address aging and age- or obesity-related conditions is far from demonstrated. Some contraindications are already known, including evidence from earlier animal studies that have shown high doses of resveratrol to affect blood platelets, which could increase the risk of bleeding when taken with anticoagulant, anti-platelet or nonsteroidal anti-inflammatory drugs.

In addition to scientists from the NIA and Harvard Medical School, researchers from the following institutions collaborated in this study: Pennington Biomedical Research Center in Baton Rouge, La., Harvard Medical School in Boston, Mass., the University of Sydney in Australia, Johns Hopkins University in Baltimore, Md., Universidad Pablo de Olavide in Sevilla, Spain, the Salk Institute in La Jolla, Calif., and Sirtris Pharmaceuticals of Cambridge, Mass., which is developing therapeutics to modulate sirtuins. Sirtris Pharmaceuticals was founded by Harvard University co-lead author David A. Sinclair.

De Cabo is a scientist in the NIA's Intramural Research Program. In addition, the work was funded by grants from the NIA, the primary supporter of the work, as well as grants from the National Institute of General Medical Sciences and the National Institute of Diabetes and Digestive and Kidney Diseases at the NIH. The Ellison Medical Research Foundation, the American Heart Foundation, the Australian and Spanish governments, the American Diabetes Association and Paul F. Glenn and The Paul F. Glenn Laboratories for the Biological Mechanisms of Aging also provided support to members of the research team.

The NIA leads the federal effort supporting and conducting research on aging and the medical, social and behavioral issues of older people. For more information on research and aging, go to www.nia.nih.gov. Publications on research and on a variety of topics of interest on health and aging can be viewed and ordered by visiting the NIA Web site, or can be ordered by calling toll-free 1-800-222-2225.


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Reference: Baur, J., Pearson, K *et al.* *Nature*, 2006 Resveratrol improves health and increases survival of mice on a high-calorie diet *Nature* 2006. DOI 10.1038/nature05354



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